



# Preconception exposures and adverse pregnancy, birth and postpartum outcomes: Umbrella review of systematic reviews

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## Abstract

**Background:** Preconception exposures have been associated with adverse pregnancy, birth and postpartum outcomes. However, the reports, statements and guidelines of national and international health organisations vary in what they recommend individuals should monitor, avoid, reduce or practise in the preconception period.

**Objectives:** To synthesise and evaluate the evidence across systematic reviews for associations between exposures before conception and adverse pregnancy, birth and postpartum outcomes.

**Data sources:** MEDLINE, Embase, Epistemonikos (to May 2020) and reference lists of included reviews, without language or date restrictions.

**Study selection, data extraction and synthesis:** Systematic literature reviews of observational and/or interventional studies reporting associations between preconception exposures in women and/or men of reproductive age and pregnancy, birth or postpartum health outcomes were included. The methodological quality of reviews and the certainty of the evidence underlying each exposure-outcome association were assessed using AMSTAR 2 and the GRADE approach.

**Results:** We identified 53 eligible reviews reporting 205 unique exposure-outcome associations. Methodological quality was generally low with only two reviews rated as 'high' quality and two as 'moderate'. We found high-certainty, randomised trial evidence that maternal folate supplementation reduces the risk of neural tube defects and anomaly-related terminations. Moderate-certainty, observational evidence was found that maternal physical activity is associated with reduced risk of pre-eclampsia and gestational diabetes, and that paternal age of  $\geq 40$  years and maternal body mass index (BMI) and interpregnancy weight gain are associated with increased risk of various adverse pregnancy and birth outcomes. Low- and very low-certainty evidence was found for other associations.

**Conclusions:** Clinicians and policymakers can be confident that maternal folate supplementation should be encouraged during the preconception period. There is moderate certainty in the evidence base that maternal physical activity, BMI and

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interpregnancy weight gain and advanced paternal age are important preconception considerations. High-quality research is required to better understand other exposure-outcome associations.

#### KEYWORDS

GRADE approach, preconception care, pregnancy, pregnancy outcome, systematic review

## 1 | BACKGROUND

Adverse pregnancy, birth and postpartum outcomes continue to have a substantial impact on morbidity and mortality. Worldwide, there are around 23 million miscarriages,<sup>1</sup> 14.8 million live preterm births,<sup>2</sup> 295,000 neonatal deaths due to congenital anomalies<sup>3</sup> and 295,000 maternal deaths due to pregnancy or childbirth complications each year.<sup>4</sup> Social, demographic, environmental and biomedical exposures before conception have been associated with these outcomes as well as longer-term offspring health and developmental outcomes.<sup>5-7</sup> However, a recent review by Schoenaker et al.<sup>8</sup> found that the clinical guidelines, position statements and policy reports of national and international health organisations vary in the preconception exposures they name as being important. Moreover, many of these guidelines, statements and reports fail to define the criteria used to determine exposure eligibility or evaluate the quality and strength of the evidence supporting the associations of these exposures with adverse outcomes.

Systematic reviews—considered the gold standard method of retrieving, synthesising and appraising all available, relevant evidence for clinical questions<sup>9</sup>—are commonly used to inform the creation of guidelines and position statements and play an important role in clinical decision-making and evidence-based healthcare.<sup>10</sup> While many systematic reviews reporting associations between preconception exposures and adverse pregnancy, birth and postpartum outcomes may exist, these are likely to vary in their scope and quality, and may present conflicting findings.<sup>11</sup> For instance, while a systematic review by Rumbold et al. concluded that maternal periconception vitamin supplementation does not affect the risk of stillbirth,<sup>12</sup> a later systematic review reported an association between this exposure and reduced stillbirth risk.<sup>13</sup>

To offer researchers, clinicians and policymakers an overview of the complete body of systematic review evidence in this area, we synthesised the findings, quality and certainty of the evidence reported in systematic reviews of interventional and/or observational studies investigating the link between preconception exposures and adverse pregnancy, birth and postpartum health outcomes.

## 2 | METHODS

The umbrella review (systematic review of systematic reviews) was prospectively registered with PROSPERO (registration number CRD42020196511) and is reported following PRISMA guidelines.<sup>14</sup>

### Synopsis

#### Study question

What is the certainty of the evidence across systematic reviews for associations between preconception exposures and adverse pregnancy, birth and postpartum outcomes?

#### What's already known

Preconception exposures have been associated with adverse pregnancy, birth and postpartum outcomes. However, the clinical guidelines, position statements and policy reports of national and international health organisations vary in what they recommend in the preconception period, creating uncertainty for clinicians, policymakers and patients.

#### What this study adds

This review has identified high- and moderate-certainty evidence that maternal preconception folate supplementation, body mass index, interpregnancy weight change and physical inactivity as well as advanced paternal age are associated with adverse pregnancy, birth and postpartum outcomes.

Review board approval was not required as this is a review of publicly available literature.

## 2.1 | Data sources

We searched MEDLINE, the systematic review repository Epistemonikos and the Cochrane Library databases from their inception to 21 May 2020. We combined relevant medical subject heading (MeSH) terms and word variants for 'preconception,' 'periconception,' 'interpregnancy' and 'contemplating pregnancy' with the Centre for Reviews and Dissemination's Search Strategy (2.1) for retrieving systematic reviews and meta-analyses<sup>15</sup> and a 'sensitivity-and-precision-maximising strategy' for retrieving overviews of systematic reviews.<sup>16</sup> This search strategy was developed with a subject librarian for use in MEDLINE (Table S1) and was then

adapted for use in Epistemonikos and the Cochrane Library. No language, publication date, ethnicity or parity restrictions were applied. Where the full texts of eligible reviews were unavailable, their authors were contacted to request these. The reference lists of eligible reviews were also hand-searched to identify additional relevant articles.

## 2.2 | Study selection and data extraction

The eligibility criteria were informed by the PECOS (population, exposure, comparison, outcomes and study designs) framework presented in Table 1. We included systematic reviews of observational and/or interventional studies. In line with the definition detailed in the Cochrane handbook for systematic reviews,<sup>17</sup> these needed to report: the eligibility criteria used for study inclusion, a pre-defined, specific research question(s), a transparent and systematic methodology (i.e. a reproducible search strategy with specific search terms provided), an analysis (meta- or narrative) including all retrieved, eligible studies and an assessment of the validity (i.e. risk of bias) of all included studies. Reviews were required to include at least two studies, involving adult ( $\geq 16$  years) women and/or men, that reported an exposure(s) occurring before conception and its association with a child and/or maternal pregnancy, birth or (up to six weeks) postpartum health outcome(s), relative to absence or lower dose(s) of the exposure.

Exposures that continued into the broader periconceptional period—defined as the time before and up to 10 weeks after conception—were eligible if the exposure clearly began before conception and preconception-specific results were not reported separately (e.g. periconceptional folic acid supplementation).<sup>18</sup> Maternal weight measured in the first trimester or at the first antenatal appointment was also eligible, as this has been found to be a valid proxy measure of pre-pregnancy weight due to minimal gestational weight gain during this period.<sup>19</sup> As specific guidelines exist for exposures and outcomes unique to fertility (e.g. assisted reproduction, sperm count, pregnancy rate),<sup>20</sup> prescription-only medication,<sup>21</sup> and specific patient groups such as women with pregestational diabetes,<sup>22</sup> asthma, depression, epilepsy, human immunodeficiency virus (HIV) and thyroid disorders,<sup>23</sup> these were excluded.

TABLE 1 PECOS framework

Population	All women and men of reproductive age ( $\geq 16$ years)
Exposure	Exposure, as defined by the review authors, occurring in the period before conception
Comparison	Absence or lower dose(s) of the exposure, as defined by the review authors
Outcome	Infant or maternal pregnancy, birth or (subacute) postpartum health outcome
Study design	Systematic review of observational and/or interventional studies

To identify articles of potential relevance, two reviewers independently screened the first 10% of abstracts against the eligibility criteria in a 'pilot phase',<sup>24</sup> to identify any divergences in interpretation of the criteria. Disagreements were discussed and resolved by consensus after consulting the protocol. As the agreement was 92%, the remaining 90% were screened by the lead reviewer. This process was repeated at the full-text review stage, where agreement between both reviewers was 98%. The lead reviewer therefore solo-reviewed the remaining texts, coding each as either eligible or ineligible and providing a reason if the latter. The list of exclusion decisions is provided as a supplementary file. A data collection spreadsheet was then piloted by both reviewers using a 10% sample of eligible reviews. No divergences were identified, and the lead reviewer therefore performed the remaining data collection alone, with the completed spreadsheet reviewed by the remaining investigators.

We extracted data on: review publication year, databases searched, eligibility and search restrictions, preconception exposures and eligible outcomes investigated, included primary studies and their design, country (categorised by income according to the World Bank classification<sup>25</sup>), comparators, covariates and review author-assigned quality rating. We also extracted pooled summary statistics (e.g. estimates of association and uncertainty, corresponding descriptive statistics, the number of participants and events). Adjusted estimates were prioritised where these were reported without missing information. Where data were missing, review authors were contacted for additional information, which was supplemented as required.

## 2.3 | Overlapping reviews

There were a number of 'overlapping reviews', where multiple systematic reviews addressed identical or near-identical research questions with many of the same primary studies included. To avoid bias through double-counting of outcome data, Cochrane's 'evidence-based decision tool' was used.<sup>11</sup> If an eligible Cochrane Review comprehensively covered the available literature for a relevant exposure-outcome association in the same population and setting, only this was included, as Cochrane endeavours not to publish multiple reviews on any given topic.<sup>11</sup> If an eligible Cochrane Review either did not exist or was not all-inclusive, all non-overlapping reviews were retained and the overlapping review covering the greatest number of studies for the association in question was used in order to maximise the amount of outcome data included in the review while still avoiding the issue of review overlap.<sup>11</sup>

## 2.4 | Quality of included reviews

The methodological quality of included reviews was assessed using the AMSTAR 2 tool, which has been validated for use with systematic reviews of both randomised and non-randomised studies.<sup>26</sup> Each review was assigned an overall quality rating of critically low,



low, medium or high quality based on its ratings on applicable items of the tool's 16 quality criterion.<sup>26</sup> Some of these items, such as whether included studies were described in 'adequate' detail, have been criticised for being susceptible to subjective opinions and biases.<sup>27</sup> The methodological quality of the first 10% of included reviews—sorted alphabetically by first author surname—was therefore assessed by two reviewers to identify any divergences in interpretation of the item criteria. Disagreements were discussed and resolved by consensus after consulting the protocol. As inter-rater agreement across the tool's 16 criteria was 82.3% overall, the remaining 90% were reviewed by the lead reviewer alone.

## 2.5 | Quality of evidence in included reviews

We used the GRADE approach<sup>28</sup>—the most widely used systematic framework for assessing evidence quality<sup>29</sup>—to rate each identified exposure-outcome association as being of either high, moderate, low or very low certainty depending on the likelihood that the true effect differs substantially from the reported estimate. As per GRADE guidance,<sup>28</sup> randomised controlled trial evidence was initially assigned a high rating and, due to likely residual confounding, evidence involving observational data was initially rated as low. This rating was then either decreased or increased by a maximum of two levels after accounting for issues relating to: risk of bias, imprecision,

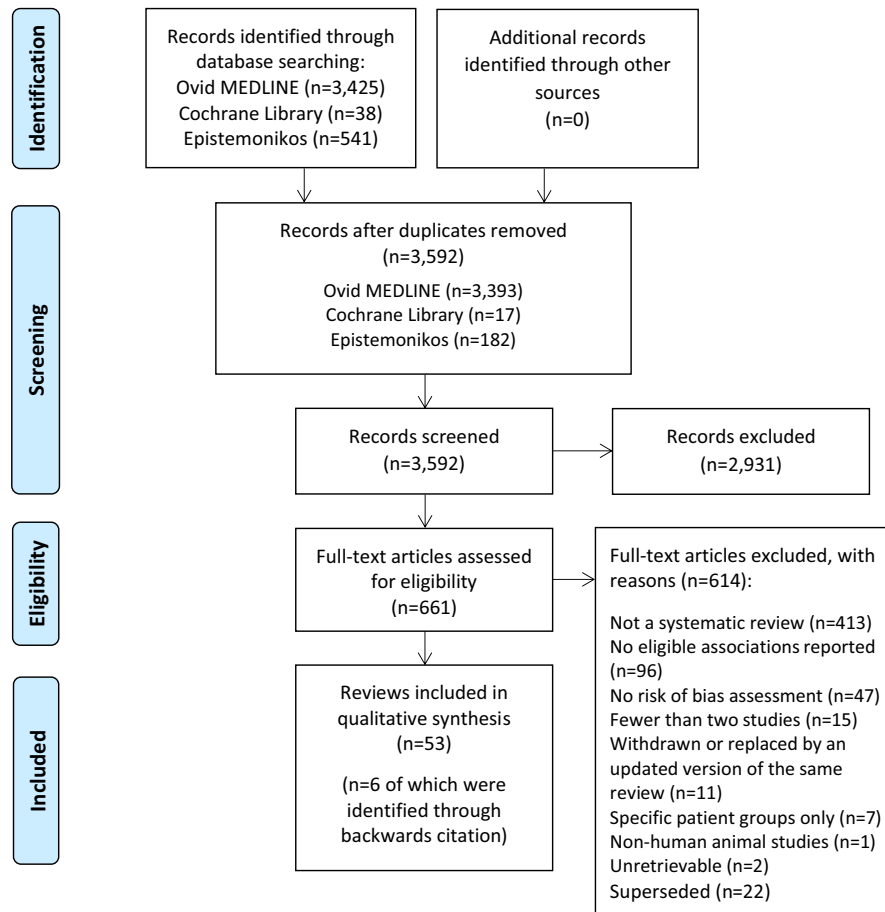
inconsistency, indirectness, publication bias, magnitude of effect, dose-response effects and residual confounding.<sup>29</sup> Further information on how decisions were made for each of these eight domains can be found in Table S2. The completed GRADE decisions spreadsheet was reviewed by all investigators. For transparency we have presented the decisions made for each review across each GRADE domain in Table S3.

## 3 | RESULTS

The PRISMA flow diagram<sup>30</sup> in Figure 1 shows that we identified 4,004 articles and screened 3,592 abstracts. Of the 661 articles that underwent full-text screening, 592 were ineligible and 22 were removed as they reported only associations covered by more comprehensive or Cochrane Reviews (see Table S4), resulting in 47 reviews being included.<sup>12,31-76</sup> Six eligible reviews were identified through citation tracking,<sup>77-82</sup> resulting in a final sample of 53 reviews.

### 3.1 | Review characteristics

The characteristics of the 53 reviews, including the number of databases and range of publication years searched, eligibility criteria and preconception exposures reported, are presented in Table S5.



**FIGURE 1** PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) flow diagram

Included reviews were published between 2005 and 2020, with the publication dates for their included studies ranging from 1973 to 2019. Two were published in Portuguese<sup>40,80</sup> and therefore translated to English, with the remainder published in English. There were 205 exposure-outcome associations reported across 1,383 studies. Twelve of these associations were based on clinical and/or randomised trials, and five included evidence from a combination of trials and observational studies. The remainder relied on observational studies only. A total of 994 (71.9%) primary studies were conducted in high-income countries and 355 in low- and middle-income countries.

### 3.2 | Methodological quality of included studies and certainty of the evidence

Two included reviews were rated as 'high'-quality,<sup>12,41</sup> two as 'moderate',<sup>38,61</sup> 11 as 'low'<sup>36,39,42,50,51,57,60,63,68,73,77</sup> and the remaining 38 as 'critically low' (Table S6). The most common 'critical' methodological concerns were lack of: appropriate methods for combining results (76.9% of relevant reviews—primarily due to a lack of justification for combining data in a meta-analysis and/or combining unadjusted estimates), justification for study exclusions (76.9%), comprehensive literature search (59.6%) and evidence of *a priori* establishment of review methods (50.0%). Two exposure-outcome associations were rated as 'high'-certainty, 27 as 'moderate', 56 as 'low' and 120 as 'very low' (Table S3). Risk of bias was the most common reason for downgrading evidence certainty.

### 3.3 | Synthesis of results

Figures 2-6 show the exposure-outcome associations, grouped by their exposure domain, along with key information such as whether the exposure continued into the broader periconceptional period and whether the included studies had observational or interventional designs. Associations that were assigned a 'very low' GRADE rating are not included in the figures or in the narrative synthesis below, as very little confidence can be had in these findings.<sup>83</sup> A summary of the findings for all 205 associations, regardless of GRADE rating, can be found in Table S7. Of the 205 associations identified, 191 (93.2%) relate to maternal exposures. These include pre-pregnancy body mass index (BMI; 75 associations), interpregnancy or birth intervals (23), interpregnancy weight change (18), age (14), folate supplementation (11), diet and nutrition (10), parity and education (seven each), physical activity (five), abuse or neglect, over-the-counter drugs and environmental exposures (four each), smoking (active or passive exposure), other vitamin supplementation and immigration status (two each), and vaccination, alcohol consumption and ethnicity (one each). The remaining 14 (6.8%) associations are related to the paternal exposures of age (10) and alcohol consumption (four).

For associations relating to BMI, the reference group was 'normal' BMI (20–24.9 kg/m<sup>2</sup>) and underweight, overweight and obesity

corresponded to BMI values of <20, 25.0–29.9 and ≥30 kg/m<sup>2</sup> unless otherwise stated. Adjusted risk estimate is used where review authors combined adjusted odds ratios, hazard ratios and rate ratios without converting them to a single measure of association.

#### 3.3.1 | Health behaviours and wider determinants of health

Figure 2 shows there is high-certainty evidence that maternal folate supplementation (<0.4–4 mg) beginning preconceptionally and terminating before 12 weeks' of gestation, relative to no intervention/supplementation or placebo, reduces the risk of both neural tube defects (risk ratio [RR] 0.31, 95% confidence interval [CI] 0.17, 0.58) and pregnancy termination for a foetal anomaly (RR 0.29, 95% CI 0.15, 0.56).<sup>41</sup> Moderate-certainty evidence was found that maternal preconception physical activity is associated with a reduced risk of both pre-eclampsia (adjusted RR 0.65, 95% CI 0.47, 0.89; highest vs lowest level of activity)<sup>33</sup> and gestational diabetes mellitus (odds ratio 0.70, 95% CI 0.57, 0.85; any vs no activity).<sup>59</sup>

Low-certainty evidence was found that maternal periconception folate supplementation is associated with a reduced risk of preterm birth<sup>54</sup> and that there is limited evidence of associations between this exposure and the risk of twinning, miscarriage, low birthweight, congenital heart defects and birth defects other than neural tube and congenital heart defects and cleft lip and palate.<sup>41</sup> Low-certainty evidence was also found that maternal vitamin supplementation (any) beginning preconceptionally and terminating in the first trimester does not affect the risk of either miscarriage or stillbirth,<sup>12</sup> and that paternal consumption of any alcohol in the 3 months before conception is associated with an increased risk of congenital heart defects.<sup>76</sup> Further low-certainty evidence was found for associations between maternal preconception iron intake and an increased risk of gestational diabetes mellitus,<sup>59</sup> adherence to a Mediterranean or High Alternate Healthy Eating Index diet and a reduced risk of gestational diabetes mellitus,<sup>59</sup> and maternal experience of abuse (physical, emotional or sexual) at any time before pregnancy and an increased risk of low birthweight.<sup>61</sup>

#### 3.3.2 | Demographic and reproductive exposures

Figure 3 shows moderate-certainty evidence that paternal age of ≥40 years is associated with a greater risk of miscarriage, and low-certainty evidence that paternal age of 35–39 years may not be associated with greater or reduced risk of this outcome.<sup>42</sup> Low-certainty evidence was found that paternal age of <20 years is associated with an increased risk of spina bifida,<sup>51</sup> that maternal age of ≥35 years is associated with a greater risk of urinary incontinence,<sup>36</sup> and that maternal age of ≥45 years is associated with increased risk of: an abnormal five-minute Apgar score, foetal loss, pregnancy complications and caesarean delivery, relative to maternal age of <45 years.<sup>52</sup> Low-certainty evidence was also found that interpregnancy intervals

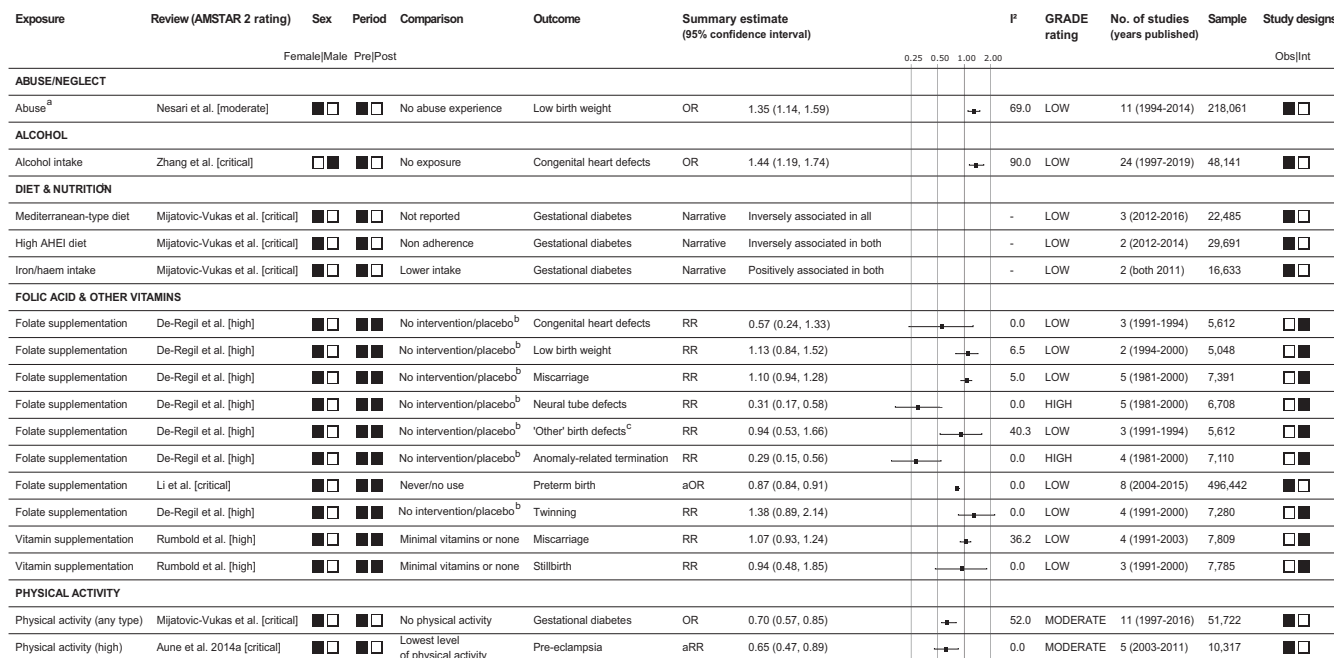


FIGURE 2 Health behaviour and wider determinants of health exposures and their associations with adverse pregnancy, birth and postpartum outcomes (high, moderate and low GRADE ratings only). Legend: Pre, Preconception; Post, Postconception; Obs, Observational; Int, Interventional; (a)OR, (adjusted) Odds ratio; AHEI, Alternative Healthy Eating Index; RR, Risk ratio. <sup>a</sup>Physical, emotional or sexual; <sup>b</sup>Or other vitamins/minerals; <sup>c</sup>Excluding neural tube and congenital heart defects and cleft lip and palate

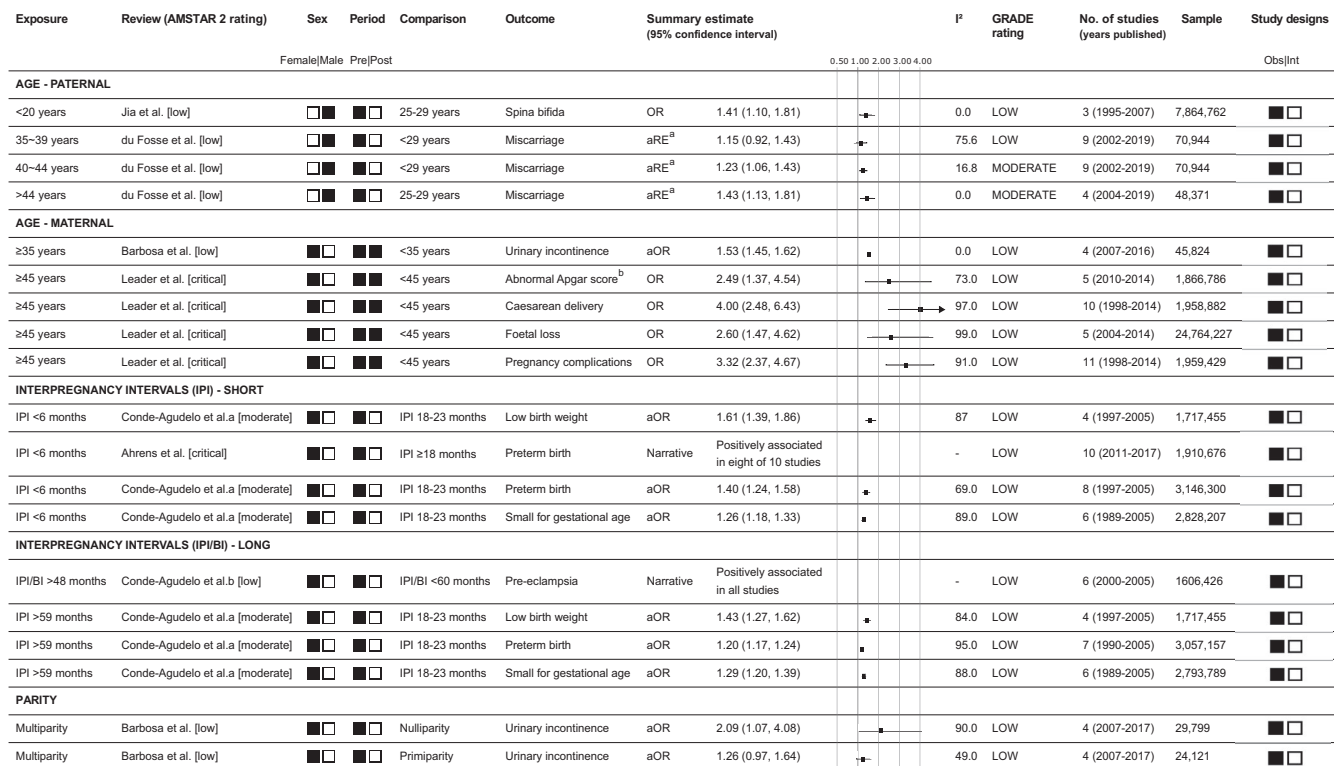


FIGURE 3 Reproductive and demographic preconception exposures and their associations with adverse pregnancy, birth and postpartum outcomes (high, moderate and low GRADE ratings only). Legend: Pre, Preconception; Post, Postconception; Obs, Observational; Int, Interventional; (a)OR, (adjusted) Odds ratio; aRE, Adjusted risk estimate; IPI, Interpregnancy interval; BI, Birth interval. <sup>a</sup>Combined adjusted odds ratios, hazard ratios and rate ratios; <sup>b</sup>At five minutes postpartum

shorter than 6 months are associated with an increased risk of low weight, small-for-gestational-age and preterm births, and that interpregnancy intervals of  $\geq 60$  months are also associated with an increased risk of these outcomes.<sup>38</sup> Further low-quality evidence was found that interpregnancy or birth intervals of  $>48$  months are associated with a greater risk of pre-eclampsia<sup>39</sup> and that multiparity is associated with an increased risk of urinary incontinence, relative to nulliparity but not primiparity.<sup>36</sup>

### 3.3.3 | Pre-pregnancy body mass index (BMI)

Figure 4 shows moderate-certainty evidence that maternal BMI in the overweight (BMI 25–29) and obese (BMI  $>30$ ) ranges is associated with a greater risk of gestational diabetes mellitus,<sup>74</sup> pregnancy-induced antenatal hypertension<sup>65</sup> and pre-eclampsia<sup>81</sup> and a reduced risk of placental abruption.<sup>31</sup> Moderate-certainty evidence was also found that maternal obesity is associated with an increased risk of foetal distress,<sup>82</sup> shoulder dystocia (vs BMI  $<30$ ),<sup>75</sup> foetal macrosomia (vs BMI 18.5–24.9)<sup>56</sup> and large for gestational age births (vs BMI  $<25$ ).<sup>44</sup> Further moderate-certainty evidence was found that, relative to the lowest category of BMI, increasing maternal BMI is associated with a greater risk of both miscarriage and neonatal death,<sup>77</sup> and that maternal underweight (BMI  $<18.5$ ) is associated with a reduced risk of pregnancy-induced hypertension.<sup>65</sup>

Figure 5 shows low-certainty evidence that maternal underweight is associated with a reduced risk of pre-eclampsia,<sup>81</sup> gestational diabetes mellitus,<sup>74</sup> large-for-gestational-age and macrosomic births<sup>56</sup> and an increased risk of small-for-gestational age birth<sup>55</sup>

and placental abruption.<sup>31</sup> Regarding maternal overweight, low-certainty evidence suggested associations between this exposure and an increased risk of foetal distress,<sup>82</sup> large-for-gestational-age and macrosomic births<sup>56</sup> and a reduced risk of small-for-gestational-age birth.<sup>56</sup> Further low-certainty evidence was found that maternal overweight and obesity are both associated with an increased risk of miscarriage,<sup>35</sup> post-term pregnancy and a longer hospital stay<sup>82</sup> and that maternal obesity, specifically, is associated with an increased risk of maternal depression,<sup>60</sup> failure to progress in labour, caesarean delivery, a low Apgar score at five minutes postpartum<sup>82</sup> and neonatal intensive care unit admission.<sup>56</sup>

### 3.3.4 | Interpregnancy weight change

Figure 6 shows moderate-certainty evidence that maternal interpregnancy weight gain of  $>2$  BMI units, relative to BMI maintenance (change of  $\leq 2$  units), is associated with a greater risk of gestational hypertension,<sup>57</sup> and that interpregnancy weight gains of both 1 to  $<3$  and  $\geq 3$  BMI units, relative to BMI maintenance ( $\leq 1$  unit change), are associated with greater risk of caesarean delivery,<sup>63,73</sup> large-for-gestational-age birth<sup>73</sup> and gestational diabetes mellitus.<sup>72</sup> Low-certainty evidence was found that: interpregnancy BMI losses and gains of  $>1$  unit are associated with an increased and reduced risk of small-for-gestational-age birth, respectively<sup>63</sup>; that interpregnancy BMI reduction of  $>1$  unit is associated with an increased risk of preterm birth and a reduced risk of large-for-gestational-age birth<sup>73</sup>; and that interpregnancy weight gain of  $>2$  units is associated with an increased risk of pre-eclampsia.<sup>57</sup>

Exposure	Review (AMSTAR rating)	Sex	Period	Comparison	Outcome	Summary estimate (95% confidence interval)	I <sup>2</sup>	GRADE rating	No. of studies (years published)	Sample	Study designs	
												Female Male
<b>UNDERWEIGHT</b>												
Underweight <sup>a</sup>	Rahman et al. [critical]	■□	■	'Normal' BMI	Antenatal hypertension <sup>b</sup>	OR 0.50 (0.40, 0.61)	0.0	MODERATE	5 (2005-2013)	37,577	■□	
<b>OVERWEIGHT / OBESITY</b>												
Increasing BMI	Aune et al.b [low]	■□	■	Lowest category of BMI	Neonatal death	aRR 1.15 (1.07, 1.23)	78.5	MODERATE	12 (2005-2014)	3,321,555	■□	
Increasing BMI	Aune et al.b [low]	■□	■	Lowest category of BMI	Miscarriage	aRR 1.16 (1.07, 1.26)	33.0	MODERATE	5 (1992-2011)	138,924	■□	
Overweight <sup>a</sup>	Rahman et al. [critical]	■□	■	'Normal' BMI	Antenatal hypertension <sup>b</sup>	OR 2.27 (2.01, 2.56)	0.1	MODERATE	5 (2005-2013)	40,140	■□	
Obesity <sup>a</sup>	Rahman et al. [critical]	■□	■	'Normal' BMI	Antenatal hypertension <sup>b</sup>	OR 5.61 (4.86, 6.46)	0.0	MODERATE	5 (2005-2013)	34,358	■□	
Obesity <sup>a</sup>	Heslehurst et al. [critical]	■□	■	'Ideal' BMI	Foetal distress	OR 1.74 (1.67, 1.81)	87.7	MODERATE	6 (1998-2007)	628,337	■□	
BMI ~25-29.9 kg/m <sup>2</sup>	Torloni et al. [critical]	■□	■	BMI 20-24.9 kg/m <sup>2</sup>	Gestational diabetes	OR 1.97 (1.77, 2.19)	55.6	MODERATE	17 (1995-2007)	395,338	■□	
BMI $>30$ kg/m <sup>2</sup>	Torloni et al. [critical]	■□	■	BMI 20-24.9 kg/m <sup>2</sup>	Gestational diabetes	OR 3.76 (3.31, 4.28)	72.8	MODERATE	31 (1992-2007)	364,668	■□	
BMI $\geq 30$ kg/m <sup>2</sup>	Gaudet et al. [critical]	■□	■	BMI $<25$ kg/m <sup>2</sup>	Large for gestational age	OR 2.42 (1.16, 2.72)	97.0	MODERATE	13 (1995-2011)	1,234,580	■□	
BMI $\geq 30$ kg/m <sup>2</sup>	Liu et al.b [critical]	■□	■	BMI 18.5-24.9 kg/m <sup>2</sup>	Macrosomia	OR 2.92 (2.67, 3.20)	0.0	MODERATE	23 (2000-2015)	93,017	■□	
BMI 25-29.9 kg/m <sup>2</sup>	Adane et al. [critical]	■□	■	BMI 18.5-24.9 kg/m <sup>2</sup>	Placental abruption	OR 0.84 (0.76, 0.93)	0.0	MODERATE	7 (2013-2019)	595,439	■□	
BMI $\geq 30$ kg/m <sup>2</sup>	Adane et al. [critical]	■□	■	BMI 18.5-24.9 kg/m <sup>2</sup>	Placental abruption	OR 0.77 (0.68, 0.87)	28.2	MODERATE	7 (2009-2019)	595,809	■□	
BMI ~25-29.9 kg/m <sup>2</sup>	Wang et al. [critical]	■□	■	BMI ~20-24.9 kg/m <sup>2</sup>	Pre-eclampsia	aRR 1.70 (1.60, 1.81)	29.4	MODERATE	10 (1997-2012)	944,324	■□	
BMI ~30-34.9 kg/m <sup>2</sup>	Wang et al. [critical]	■□	■	BMI ~20-24.9 kg/m <sup>2</sup>	Pre-eclampsia	aRR 2.93 (2.58, 3.33)	66.6	MODERATE	9 (1997-2012)	172,0331	■□	
BMI $\geq 35$ kg/m <sup>2</sup>	Wang et al. [critical]	■□	■	BMI ~20-24.9 kg/m <sup>2</sup>	Pre-eclampsia	aRR 4.14 (3.61, 4.75)	0.0	MODERATE	4 (2004-2012)	863,221	■□	
BMI $\geq 30$ kg/m <sup>2</sup>	Zhang et al. [critical]	■□	■	BMI $<30$ kg/m <sup>2</sup>	Shoulder dystocia	aRR 1.76 (1.12, 2.77)	50.4	MODERATE	6 (2003-2016)	162,827	■□	

FIGURE 4 Pre-pregnancy weight/BMI exposures and their associations with adverse pregnancy, birth and postpartum outcomes (moderate GRADE ratings only). Legend: Pre, Preconception; Post, Postconception; Obs, Observational; Int, Interventional; BMI, Body mass index; OR, Odds ratio; aRR, Adjusted risk ratio. <sup>a</sup>Author defined; <sup>b</sup>Pregnancy-induced

Exposure	Review (AMSTAR 2 rating)	Sex	Period	Comparison	Outcome	Summary estimate (95% confidence interval)	I <sup>2</sup>	GRADE rating	No. of studies (years published)	Sample	Study design	Obs Int	
												Female Male	Pre Post
<b>UNDERWEIGHT</b>													
BMI <20 kg/m <sup>2</sup>	Torloni et al. [critical]	■□	■	BMI 20-24.9 kg/m <sup>2</sup>	Gestational diabetes	OR 0.75 (0.69, 0.82)		16.8	LOW	16 (1997-2007)	356,403	■□	
BMI <20 kg/m <sup>2</sup>	Wang et al. [critical]	■□	■	BMI 20-24.9 kg/m <sup>2</sup>	Pre-eclampsia	aRR 0.77 (0.63, 0.95)		52.5	LOW	6 (1999-2009)	99,015	■□	
BMI ≤18.5 kg/m <sup>2</sup>	Liu et al. b [critical]	■□	■	BMI 18.5-24.9 kg/m <sup>2</sup>	Large for gestational age	OR 0.52 (0.44, 0.61)		45.8	LOW	9 (2001-2013)	103,415	■□	
BMI ≤18.5 kg/m <sup>2</sup>	Liu et al. b [critical]	■□	■	BMI 18.5-24.9 kg/m <sup>2</sup>	Macrosomia	OR 0.55 (0.47, 0.63)		34.2	LOW	28 (2001-2014)	170,484	■□	
BMI <18.5 kg/m <sup>2</sup>	Adane et al. [critical]	■□	■	BMI 18.5-24.9 kg/m <sup>2</sup>	Placental abruption	OR 1.38 (1.12, 1.70)		55.2	LOW	7 (2010-2019)	595,546	■□	
BMI <18.5 kg/m <sup>2</sup>	Liu et al. a [critical]	■□	■	BMI 18.5-24.9 kg/m <sup>2</sup>	Small for gestational age	OR 1.75 (1.51, 2.02)		80.0	LOW	10 (2005-2016)	170,569	■□	
<b>OVERWEIGHT / OBESITY</b>													
Obesity <sup>a</sup>	Molyneux et al. [low]	■□	■	'Normal' weight	Antenatal depression	OR 1.43 (1.27, 1.61)		44.4	LOW	28 (2000-2013)	47,929	■□	
Obesity <sup>a</sup>	Heslehurst et al. [critical]	■□	■	'Ideal' BMI	Caesarean delivery	OR 2.00 (1.87, 2.15)		0.0	LOW	16 (1995-2006)	>58,429	■□	
Obesity <sup>a</sup>	Heslehurst et al. [critical]	■□	■	'Ideal' BMI	Failure to progress in labour	OR 2.31 (1.87, 2.84)		50.9	LOW	3 (1998-2007)	14,721	■□	
Overweight <sup>a</sup>	Heslehurst et al. [critical]	■□	■	'Ideal' BMI	Foetal distress	OR 2.06 (1.44, 2.96)		0.0	LOW	4 (2004-2007)	6,469	■□	
Overweight <sup>a</sup>	Heslehurst et al. [critical]	■□	■	'Ideal' BMI	Hospital stay (length of)	OR 2.56 (2.46, 2.67)		88.6	LOW	4 (1995-2006)	>9,511	■□	
Obesity <sup>a</sup>	Heslehurst et al. [critical]	■□	■	'Ideal' BMI	Hospital stay (length of)	OR 2.84 (2.77, 2.91)		94.4	LOW	4 (1995-2006)	>20,414	■□	
Obesity <sup>a</sup>	Heslehurst et al. [critical]	■□	■	'Ideal' BMI	Low Apgar score <sup>b</sup>	OR 1.69 (1.60, 1.80)		82.2	LOW	5 (1998-2005)	760,099	■□	
Overweight <sup>a</sup>	Heslehurst et al. [critical]	■□	■	'Ideal' BMI	Post-term pregnancy	OR 1.28 (1.20, 1.37)		51.5	LOW	3 (1995-2006)	50,989	■□	
Obesity <sup>a</sup>	Heslehurst et al. [critical]	■□	■	'Ideal' BMI	Post-term pregnancy	OR 1.41 (1.38, 1.45)		78.8	LOW	4 (1995-2006)	654,753	■□	
BMI 25-29.9 kg/m <sup>2</sup>	Liu et al. b [critical]	■□	■	BMI 18.5-24.9 kg/m <sup>2</sup>	Large for gestational age	OR 1.45 (1.29, 1.63)		67.7	LOW	13 (2001-2015)	138,290	■□	
BMI 25-29.9 kg/m <sup>2</sup>	Liu et al. b [critical]	■□	■	BMI 18.5-24.9 kg/m <sup>2</sup>	Macrosomia	OR 1.70 (1.55, 1.87)		48.6	LOW	27 (2004-2015)	446,753	■□	
BMI ~25-29.9 kg/m <sup>2</sup>	Balsells et al. [critical]	■□	■	BMI ~18.5-24.9 kg/m <sup>2</sup>	Miscarriage	RR 1.09 (1.04, 1.13)		28.0	LOW	23 (2002-2016)	138,988	■□	
BMI ≥30 kg/m <sup>2</sup>	Balsells et al. [critical]	■□	■	BMI ~18.5-24.9 kg/m <sup>2</sup>	Miscarriage	RR 1.21 (1.15, 1.27)		28.0	LOW	22 (2002-2014)	121,393	■□	
BMI ≥30 kg/m <sup>2</sup>	Liu et al. b [critical]	■□	■	BMI 18.5-24.9 kg/m <sup>2</sup>	NICU admission	OR 1.91 (1.60, 2.29)		66.3	LOW	17 (1998-2015)	72,398	■□	
BMI 25-29.9 kg/m <sup>2</sup>	Liu et al. b [critical]	■□	■	BMI 18.5-24.9 kg/m <sup>2</sup>	Small for gestational age	OR 0.71 (0.66, 0.76)		37.4	LOW	11 (2001-2015)	77,726	■□	

FIGURE 5 Pre-pregnancy weight/BMI exposures and their associations with adverse pregnancy, birth and postpartum outcomes (low GRADE ratings only). Legend: Pre, Preconception; Post, Postconception; Obs, Observational; Int, Interventional; BMI, Body mass index; OR, Odds ratio; (a)RR, (adjusted) Risk ratio; NICU, Neonatal Intensive Care Unit. <sup>a</sup>Author defined; <sup>b</sup>At five minutes postpartum

Exposure	Review (AMSTAR 2 rating)	Sex	Period	Comparison	Outcome	Summary estimate (95% confidence estimate)	I <sup>2</sup>	GRADE rating	No. of studies (years published)	Sample	Study designs	Obs Int	
												Female Male	Pre Post
<b>INTERPREGNANCY WEIGHT LOSS</b>													
Loss of >1 kg/m <sup>2</sup>	Timmermans et al. [low]	■□	■□	BMI maintenance (-1 to 1 kg/m <sup>2</sup> )	Large for gestational age	aOR 0.80 (0.66, 0.98)		95.0	LOW	4 (2006-2019)	102,496	■□	
Loss of >1 kg/m <sup>2</sup>	Timmermans et al. [low]	■□	■□	BMI maintenance (-1 to 1 kg/m <sup>2</sup> )	Preterm birth	aOR 1.40 (1.08, 1.83)		72.0	LOW	2 (2014-2019)	8,406	■□	
Loss of >1 kg/m <sup>2</sup>	Oteng-Ntim et al. [low]	■□	■□	BMI maintenance (-2 to 2 kg/m <sup>2</sup> )	Small for gestational age	aOR 1.31 (1.06, 1.63)		53.5	LOW	3 (2004-2016)	49,008	■□	
<b>INTERPREGNANCY WEIGHT GAIN</b>													
Gain of >1 kg/m <sup>2</sup>	Oteng-Ntim et al. [low]	■□	■□	BMI maintenance (-2 to 2 kg/m <sup>2</sup> )	Small for gestational age	aOR 0.83 (0.70, 0.99)		56.8	LOW	3 (2004-2016)	49,008	■□	
Gain of 1-<3 kg/m <sup>2</sup>	Timmermans et al. [low]	■□	■□	BMI maintenance (-1 to 1 kg/m <sup>2</sup> )	Caesarean delivery	aOR 1.13 (1.06, 1.20)		51.0	MODERATE	4 (2006-2017)	158,364	■□	
Gain of ≥3 kg/m <sup>2</sup>	Oteng-Ntim et al. [low]	■□	■□	BMI maintenance (-2 to 2 kg/m <sup>2</sup> )	Caesarean delivery	aOR 1.72 (1.32, 2.24)		89.1	MODERATE	4 (2006-2016)	341,960	■□	
Gain of 1-<3 kg/m <sup>2</sup>	Teulings et al. [critical]	■□	■□	BMI maintenance (-1 to 1 kg/m <sup>2</sup> )	Gestational diabetes	aOR 1.51 (1.22, 1.80)		71.0	MODERATE	5 (2006-2015)	251,992	■□	
Gain of ≥3 kg/m <sup>2</sup>	Teulings et al. [critical]	■□	■□	BMI maintenance (-1 to 1 kg/m <sup>2</sup> )	Gestational diabetes	aOR 2.37 (1.40, 3.34)		91.0	MODERATE	4 (2006-2017)	234,772	■□	
Gain of 1-<3 kg/m <sup>2</sup>	Timmermans et al. [low]	■□	■□	BMI maintenance (-1 to 1 kg/m <sup>2</sup> )	Large for gestational age	aOR 1.33 (1.11, 1.60)		0.0	MODERATE	4 (2006-2019)	138,205	■□	
Gain of ≥3 kg/m <sup>2</sup>	Timmermans et al. [low]	■□	■□	BMI maintenance (-1 to 1 kg/m <sup>2</sup> )	Large for gestational age	aOR 1.54 (1.28, 1.86)		0.0	MODERATE	4 (2006-2019)	103,350	■□	
Gain of ≥2 kg/m <sup>2</sup>	Martinez-Hortelano et al. [low]	■□	■□	BMI maintenance (-2 to 2 kg/m <sup>2</sup> )	Gestational hypertension	OR 1.45 (1.11, 1.80)		76.1	MODERATE	6 (1999-2017)	239,150	■□	
Gain of ≥2 kg/m <sup>2</sup>	Martinez-Hortelano et al. [low]	■□	■□	BMI maintenance (-2 to 2 kg/m <sup>2</sup> )	Pre-eclampsia	OR 1.39 (1.18, 1.60)		39.2	LOW	5 (2006-2017)	364,943	■□	

FIGURE 6 Interpregnancy weight change exposures and their associations with adverse pregnancy, birth and postpartum outcomes (high, moderate and low GRADE ratings only). Legend: Pre, Preconception; Post, Postconception; Obs, Observational; Int, Interventional; BMI, Body mass index. (a)OR, (adjusted) Odds ratio

## 4 | COMMENT

### 4.1 | Principal findings

Our review identified 53 systematic literature reviews reporting 205 unique associations for exposures in the preconception period. Only 17 of these associations used evidence gathered from randomised trials. The methodological quality of reviews was generally poor; only two reviews were assessed as high- and two as moderate quality. The

only high-certainty findings were that maternal folate supplementation commencing preconceptionally reduces the risk of neural tube defect-affected births and pregnancy terminations for a foetal anomaly.

### 4.2 | Strengths of the study

Strengths of this review include its comprehensive search, where both observational and interventional studies were included,





exposures were not pre-specified in the search strategy, and no language, publication year or study design search restrictions were applied, resulting in the inclusion of a diverse range of exposure-outcome associations. We used the GRADE approach, which critically evaluates evidence certainty; this type of summary, which incorporates both an assessment of methodological quality and strength of the evidence base, is useful to clinical practice and policymakers.<sup>83</sup>

### 4.3 | Limitations of the data

Our review has some noted limitations. We did not search for grey literature; unpublished systematic reviews may contain further associations or cover reported associations more comprehensively. Moreover, where a Cochrane Review either did not exist or was not all-inclusive for a particular exposure-outcome association, our selection of the overlapping review containing the greatest number of studies for the association may not have reflected the most methodologically sound review and the quality of the data we have reported is ultimately constrained by the quality of the systematic reviews from which they are derived. However, as an inevitable limitation of umbrella reviews is that the included systematic reviews may not have included relevant primary studies, this approach allowed us to maximise the number of studies covered while still avoiding the issue of review overlap. Nonetheless, whether any 'missed' primary studies would have been sufficient to alter our findings remains unclear.

There also remains the possibility that some reviews have not described relevant exposures as pre-, peri- or inter-conception factors in their titles or abstracts and were therefore not identified by our search. While our use of citation tracking helped to identify some of these reviews, it is possible others may have been missed. Moreover, while the GRADE approach has been argued to reflect 'most' of the Bradford Hill criteria for establishing causality, it was not explicitly developed for this purpose.<sup>84</sup> Our GRADE ratings should therefore only be interpreted as reflecting the certainty of the evidence for reported exposure-outcome associations and not as evidence that reported exposures *cause* their associated outcome. Lastly, while we took care to report exposures occurring only within the periconceptional period, it is possible that some observed associations—particularly those derived from observational studies relating to late pregnancy or postpartum outcomes—may be at least partially attributed to an exposure's continued presence beyond the periconceptional period.

### 4.4 | Interpretation

Fewer than half of women practice preconception folate supplementation in countries such as England, Scotland and the United States,<sup>85</sup> mean paternal age at conception continues to rise in high-income countries,<sup>86,87</sup> and globally, approximately 55% of women are overweight or obese<sup>88</sup> and 31.7% are not sufficiently physically active.<sup>89</sup> The main implication of our findings for public health

policy is that there needs to be greater investment in policies and interventions to support preconception supplementation, physical activity, maintenance of a healthy weight and reproductive life planning. Improvement in these exposures is likely to reap long-term health and economic dividends.<sup>90</sup> Moreover, while the review by Schoenaker et al.<sup>8</sup> found that maternal folic acid supplementation and weight were listed in the preconception guidelines, statements and reports of five of the health organisations considered, maternal physical activity was mentioned in the guidelines, statements and reports of just three organisations, paternal age in just one and interpregnancy weight change was not mentioned in any. This policy divergence suggests that greater collaboration may be required to achieve consensus in messaging around preconception health.

The findings of this review also highlight several research gaps. Few reviews or primary studies considered the preconception health of men, with only 6.8% of reported associations relating to paternal exposures. There was also a gap in the examination of the wider determinants of physical and mental health, such as pollution, poverty and abusive relationships, relative to individual-level exposures like maternal weight and folate supplementation, where multiple systematic reviews presented overlapping data for the same outcomes. There is a need for higher-quality systematic reviews in this area, with *a priori* protocol registration, comprehensive literature searches, justified study exclusions and appropriate statistical methods. There is also a need for lower- and middle-income countries to be better represented in this research and, where possible, for more randomised controlled trials and other research seeking to establish epidemiologic evidence of causality to be conducted.

### 4.5 | Conclusions

In conclusion, we found high- and moderate-certainty evidence that maternal preconception folate supplementation, BMI, interpregnancy weight change, physical inactivity and advanced paternal age are associated with adverse pregnancy, birth and postpartum outcomes.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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